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WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
TUNGATURTHI, PARITHOSH K	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,148	SAWYER ET AL.	
	Examiner	Art Unit	
	Parithosh K. Tungaturthi	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-13 and 16-27* is/are pending in the application.

4a) Of the above claim(s) *16,17 and 20-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-13,18,19 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/3/07;10/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The applicant has timely traversed the non-final rejection in the reply filed on 04/30/2007, and a response to the arguments is set forth.

It is noted that the applicant pointed out the inconsistency in status of the pending claims (in particularly item (4a) on page 1 and item (2) on page 3 of the previous office action mailed 11/28/2006). The examiner apologizes for the inconvenience and directs the applicants to paragraphs 2-6 below for the appropriate status of the claims.

2. Claims 3 and 14-15 have been cancelled.

3. Claims 16, 17 and 20-26 have been withdrawn.

4. Claim 27 has been newly added.

5. Claims 1, 2, 4-13, 18 and 19 have been amended.

6. Claims 1, 2, 4-13, 18, 19 and 27 are under examination.

7. This office action consists of new grounds of rejection.

Foreign Priority

8. The examiner acknowledges the applicant's foreign priority claim, including the receipt of certified copies of the foreign priority documents (received on 05/26/2005).

Information Disclosure Statement

9. The information disclosure statements (IDS) submitted on 10/14/2004 and 05/03/2007 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner is considering the information disclosure statements.

Objections Withdrawn

10. The objection of claim 1 is withdrawn in view of amendments to the claim.

Rejections Withdrawn

11. The rejection of claims 18 and 19 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

12. The rejection of claims 1-9 and 13 under 35 U.S.C. 102(b) as being anticipated by Kucherlapati et al (US Patent 6150584; Date Issued: 11/21/2000) is withdrawn in view of amendments to the claims.

13. The rejection of claims 18 and 19 under 35 U.S.C. 102(b) as being anticipated by Mather et al (WO/2000/037503; Publication Date: 06/29/2000) is withdrawn in view of amendments to the claims.

14. The rejection of claims 1-15, 18 and 19 under 35 U.S.C. 103(a) as being unpatentable over Kucherlapati et al (US Patent 6150584; Date Issued: 11/21/2000) in view of Mather et al (WO/2000/037503; Publication Date: 06/29/2000) in view of Rava

et al (US Patent 6720149; Date Filed 05/28/2002, Claims priority to 10/10/1999) in view of Kessler et al (PGPUB 20030044849; Date Filed:08/21/2002, Claims priority to 10/22/2001) is withdrawn in view of amendments to the claims.

New Grounds of Rejection

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

17. Claims 1, 2, 4-13, 18, 19 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mather et al (WO/2000/037503; Publication Date: 06/29/2000) in view of Kucherlapati et al (US Patent 6150584; Date Issued: 11/21/2000) and van de Winkel et al (PGPUB 20030138421; Publication Date: 07/24/2003) and Rava et al (US

Patent 6720149; Date Filed 05/28/2002, Claims priority to 10/10/1999) and Kessler et al (PGPUB 20030044849; Date Filed:08/21/2002, Claims priority to 10/22/2001).

The instant claims are drawn to a high-throughout method for producing a plurality of monoclonal antibodies, each of binds to a different candidate antigen, said method comprising the steps of: a) introducing a plurality of candidate antigens into an animal or animals; b) recovering antibody-producing cells from said animal or animals and rendering these cells into a single cell suspension; c) generating immortalized cell lines from said single cell suspension; d) screening the supernatant of said immortalized cell lines against a protein chip or protein chips on which the candidate antigens are displayed; and (e) selecting monoclonal antibodies that bind to said candidate antigens; wherein said animal or animals is a mouse, a rat, a guinea pig or a rabbit; wherein said candidate antigen is a purified candidate antigen; wherein between two and fifty different purified candidate antigens are introduced into each animal; wherein between 0.001 and 1000 micrograms of each antigen is introduced into each animal. Further, the claims are drawn to a method of claim 1 comprising the additional step of supplying the animal or animals with a booster dose of some or all of the antigens which were introduced into the animal or animals prior to the removal of antibody-producing cells, wherein the antibody-producing cells are B cells, T cell or stem cells, wherein the antibody-producing cells are recovered by removal of spleen tissue, lymph nodes or bone marrow of the animal, wherein the immortalized cell line is a hybridoma cell line produced by somatic fusion of the cells in the single cell suspension to myeloma cells.

Claims 10-12 are draw to the method of claim 1, wherein said protein chip or protein chips is a plain-glass slide, a 3D gel pad chip, a microwell chip or a cell chip, wherein the step of detecting the monoclonal antibodies bound to the antigens further comprises isotyping the monoclonal antibodies, wherein said step of detecting and isotyping the monoclonal antibodies comprises adding isotype specific anti-immunoglobulin antibodies to said protein chip or protein chips, wherein each anti-immunoglobulin antibody having a different isotype specificity has a different label, and detecting the presence of said labels, further comprising assessing the specificity with which each isolated monoclonal antibody binds to antigen using a protein chip or chips comprising said antigen. Further claims 18 and 19 are drawn to a method for producing a plurality of monoclonal antibodies, each of which binds to a different candidate antigen, comprising introducing a plurality of candidate antigens into an animal, each purified candidate antigen being obtained from a different protein, which further comprises any of the steps recited in claim 1. In addition, claim 27 is drawn to a method of identifying a plurality of monoclonal antibodies, each of which binds to a different candidate antigen, said method comprising the steps of: a) screening the supernatant of immortalized cell lines against one or more protein chips on which the candidate antigens are displayed; and b) selecting monoclonal antibodies that bind to said candidate antigens, said method being characterized in that said immortalized cell lines are generated from a single suspension of antibody-producing cells that produce antibodies against a plurality of antigens.

Mather et al teach a method of generation of a population (interpreted as plurality) of monoclonal antibodies. Mather et al teach a method for immunizing a host mammal with a plurality of viable and intact cells of a specific type that constitute cell surface antigens anchored on the plasma membrane (background of the invention, in particular), wherein the surfaces of the cells are free of serum. Such a method of generating monoclonal antibodies (page 3 - summary of the invention, in particular) binding to the surface antigens of a specific cell type, comprises (a) immunizing a host mammal with a plurality of viable and intact cells of a specific cell type; (b) fusing lymphoid cells from the immunized mammal with an immortalized cell line to produce hybridomas that produce monoclonal antibodies; (c) culturing the hybridomas under the conditions favorable for the secretion of monoclonal antibodies; (d) selecting the hybridomas that secrete monoclonal antibodies binding to surface antigens present on the viable and intact cells used for immunization; and further (e) identifying the antigens to which the monoclonal antibodies bind to which involves the screening the said cell type for a specific binding to the monoclonal antibodies produced by the hybridoma selected in step (d) above. Mather et al teach immunization with a plurality of cells indicating that immunization of multiple candidate antigens for the production of monoclonal antibodies in a mouse, including suggesting use of other mammals such as rabbits, other murine animals, etc. Mather et al also teach that the lymphoid cells from the host, are collected after a few days after the final boost (please see page 9, in particular), indicating that a booster dosage of antigens is introduced into the animals prior to the removal of the antibody-producing cells. Mather et al further teach that the

hybridomas are prepared from the lymphocytes and immortalized cells using the general somatic cell hybridization techniques of Kohler and Millstein (which is also admitted as prior art by the applicants on page 17 of the response filed on 04/30/2007).

Mather et al does not teach the screening of the supernatant against a protein chip in addition to the isotyping of monoclonal antibodies. These deficiencies are made up for by Kucherlapati et al, van de Winkel et al, Rava et al and Kessler et al.

Kucherlapati et al teach (abstract and paragraph 18, in particular) a method of producing monoclonal antibodies comprising administering the antigen into a nonhuman animal (mouse, in this instance), obtaining B cells, typically from the spleen, but also, if desired, from the peripheral blood lymphocytes or lymph nodes and immortalizing using any of a variety of techniques; and culturing the resulting hybridomas or otherwise immortalized B cells and screen for the secretion of antibodies of the desired specificity. In Example 1, Kucherlapati et al teach that 50 micrograms of the antigen (human IL-6, in this instance) was used for immunizing the mouse intraperitoneally. Kucherlapati et al also teach preparation of high affinity human monoclonal antibodies (example 9, paragraphs 120-123, in particular), wherein the antibodies were screened for their kinetic parameters, specifically their on and off rates and their dissociation constants (Kd) by BIAcore instrument which uses plasmon resonance to measure the binding of an antibody to an antigen-coated gold chip. Kucherlapati et al also teach (paragraph 5, in particular) that it may be necessary to provide the antigen with a carrier to enhance its immunogenicity and/or to include formulations which contain adjuvants and/or to administer multiple injections and/or to vary the route of the immunization, and the like.

Van de Winkel et al teach generation of hybridomas producing monoclonal antibodies comprising generating immortalized cell line from a single cell suspension of splenic lymphocytes from immunized mice and screening for antibodies (paragraph 88, in particular).

Rava et al teach methods for concurrently processing multiple biological chip assays by providing a biological chip plate comprising a plurality of test wells, each test well having a biological chip having a molecular probe array; introducing samples into the test wells; subjecting the biological chip plate to manipulation by a fluid handling device that automatically performs steps to carry out reactions between target molecules in the samples and probes; and subjecting the biological chip plate to a biological chip plate reader that interrogates the probe arrays to detect any reactions between target molecules and probes (abstract, in particular). Rava et al teach that a probe can be selected from proteins of interest and the targets can be selected from monoclonal antibodies and the antisera reactive with specific antigenic determinants (detailed description, paragraph 3; in particular). Rava et al defines a chip as a substrate, which can be silicon or glass, having a surface to which one or more arrays of probes is attached.

Kessler et al teach that can antibodies manipulated based on antigenic or structural markers on the immunoglobulins of different animal species, classes or isotypes, subclasses, allotypes. For example, human monoclonal antibodies being screened may be distinguished from a PAL consisting of murine antibodies by use of secondary or indirect immunofluorescence or immunoenzymatic staining involving anti-

human immunoglobulin reagents. Other usable labels besides fluorescers and enzymes include radiosiotopes, chemiluminescers, phosphors, particles, etc. In addition, measurements of affinities, avidities, association rates or dissociation rates can be made directly or indirectly on the monoclonal antibodies by surface plasmon resonance (e.g., BIAcore).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have a high-throughout method for producing a plurality of monoclonal antibodies as claimed by combining the methods taught by Mather et al, Kucherlapati et al, Rava et al and Kessler et al.

Please note that the introduction of the phrase "high-throughout" into the claims does not alter the method steps or the materials used in the production of plurality of monoclonal antibodies. Further, the specification does not differentiate the "high-throughout" method of producing a plurality of monoclonal antibodies from just any method of producing a plurality of monoclonal antibodies comprising the method steps.

One of ordinary skill in the art would have been motivated and would have reasonable expectation of success to have produced a method of producing plurality of monoclonal antibodies as taught by Mather et al, because Mather et al teach a method of generating monoclonal antibodies comprising (a) immunizing a host mammal with a plurality of viable and intact cells of a specific cell type; (b) fusing lymphoid cells from

the immunized mammal with an immortalized cell line to produce hybridomas that produce monoclonal antibodies; (c) culturing the hybridomas under the conditions favorable for the secretion of monoclonal antibodies; (d) selecting the hybridomas that secrete monoclonal antibodies binding to surface antigens present on the viable and intact cells used for immunization; and further (e) identifying the antigens to which the monoclonal antibodies bind to which involves the screening the said cell type for a specific binding to the monoclonal antibodies produced by the hybridoma selected in step (d) above.

In addition, one of ordinary skill in the art would have known to combine the teachings of Mather with Kucherlapati et al and van de Winkel et al, because Kucherlapati et al teach a method of producing monoclonal antibodies comprising administering the antigen into a nonhuman animal obtaining B cells and immortalizing using any of a variety of techniques; and culturing the immortalized B cells and screen for the secretion of antibodies of the desired specificity; wherein the antibodies were screened for their kinetic parameters, specifically their on and off rates and their dissociation constants (Kd) by BIAcore instrument which uses plasmon resonance to measure the binding of an antibody to an antigen-coated gold chip and Van de Winkel et al teach generation of hybridomas producing monoclonal antibodies comprising generating immortalized cell line from a single cell suspension of splenic lymphocytes from immunized mice.

Further, one of ordinary skill in the art would have been motivated and would have had a reasonable expectation of success to have combined the above teachings

with Rava et al and Kessler et al because Rava et al teach methods for concurrently processing multiple biological chip assays by providing a biological chip plate comprising a plurality of test wells, each test well having a biological chip having a molecular probe (which can be selected from proteins of interest, for example) array; introducing samples into the test wells; subjecting the biological chip plate to manipulation by a fluid handling device that automatically performs steps to carry out reactions between target molecules (which can be selected from monoclonal antibodies, for example) in the samples and probes; and subjecting the biological chip plate to a biological chip plate reader that interrogates the probe arrays to detect any reactions between target molecules; and further because Kessler et al teach that antibodies can manipulated based on antigenic or structural markers on the immunoglobulins, for example various isotypes can be generated; in addition to teaching that human monoclonal antibodies can be distinguished by use of secondary or indirect immunofluorescence or immunoenzymatic staining involving anti-human immunoglobulin reagents, including other usable labels besides fluorescers and enzymes include radiosiotopes, chemiluminescers, phosphors, particles, etc.

Thus, it would have been obvious to one of ordinary skill in the art one would have been motivated to produce the claimed invention by using the method of producing the plurality of monoclonal antibodies as taught by Mather et al, which comprises (a) immunizing a host mammal with a plurality of viable and intact cells of a specific cell type; (b) fusing lymphoid cells from the immunized mammal with an immortalized cell line to produce hybridomas that produce monoclonal antibodies; (c)

culturing the hybridomas under the conditions favorable for the secretion of monoclonal antibodies; (d) selecting the hybridomas that secrete monoclonal antibodies binding to surface antigens present on the viable and intact cells used for immunization; and further (e) identifying the antigens to which the monoclonal antibodies bind to which involves the screening the said cell type for a specific binding to the monoclonal antibodies produced by the hybridoma selected in step (d) above, wherein the immortalized B cells can be screened using a BIAcore instrument which uses plasmon resonance to measure the binding of an antibody to an antigen-coated gold chip as taught by Kucherlapati et al, and further combining with the methods of Rava et al and Kessler et al because Rava et al teach detection of monoclonal antibodies using protein chips and Kessler et al teach the isotyping of monoclonal antibodies wherein the polyclonal antibody libraries are used to mask antigens on the target cell that are not of interest, making it easier to detect a monoclonal antibody that binds to the cell surface antigen of interest.

Furthermore, Mather et al teach immunization with a plurality of cells indicating that immunization of multiple candidate antigens for the production of monoclonal antibodies in a mouse, including suggesting use of other mammals such as rabbits, other murine animals, etc. and that the lymphoid cells from the host, are collected after a few days after the final boost, indicating that a booster dosage of antigens is introduced into the animals prior to the removal of the antibody-producing cells; in addition to that the hybridomas are prepared from the lymphocytes and immortalized cells using the general somatic cell hybridization techniques

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Applicants Arguments

Applicants argue (pages 10-11 of the response filed on 04/30/2007) that Kucherlapati et al fail to disclose or suggest immunization of animals with a plurality of antigens and does not describe immunization animals with a plurality of antigens in order to produce a monoclonal antibodies against a plurality of antigens simultanewoulsy, nor screening of immortalized cell lines against protein chips on multiple antigens.

In addition, applicants argue that Mather et al fail to disclose or suggest immunization of mammals with purified antigens ... Mather et al does not read on the instant claims because the claims also required immunization with a plurality of "purified" candidate antigens ... does not describe generating immortalized cell lines from a single suspension of antibody-producing cells" (pages 12-13 of the response filed on 04/30/2007) ... Mather teaches away and is disadvantageous ... (page 14 of the reponse).

Further, the applicants argue that Rava does not suggest that a plurality of antigens could be displayed on chips simultaneously and that Kessler does not teach that an animal or animals can be immunized with a plurality of purified antigens to produce monoclonal antibodies against a plurality of purified antigens, but is considered

with methods of producing antibodies by immunization with while cells ... (pages 15-16 of the response).

In response to the above arguments, the applicant is reminded that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Thus, it should be noted that the instant claims are considered obvious over the combination of all the references cited, and not based on only one individual reference.

As discussed above, Mather et al teach the method of producing a plurality of monoclonal antibodies, Kucherlapati et al teach the method of screening monoclonal antibodies using antigen-coated gold chip, Van de Winkel et al teach generation of hybridomas producing monoclonal antibodies comprising generating immortalized cell line from a single cell suspension of splenic lymphocytes from immunized mice, Rava et al teach the method of processing multiple biological chip assays to detect any reactions between target molecules and probes, wherein probe can be selected from proteins of interest and the targets can be selected from monoclonal antibodies, and Kessler et al teach that human monoclonal antibodies may be distinguished, based on

antigenic or structural markers on the immunoglobulins of isotypes, by use of secondary or indirect immunofluorescence or immunoenzymatic staining involving anti-human immunoglobulin reagents.

Thus, it is a combination of the teachings of Mather et al, Kucherlapati et al, Van de Winkel, Rava et al and Kessler et al that would motivate one of ordinary skill in the art and an based on such combination would one of ordinary skill in the art have a reasonable expectation of success to produce the claimed method of production of a plurality of monoclonal antibodies.

Further, the applicant is directed to Mather et al (page 5, in particular) wherein "a population of monoclonal antibodies" is defined as a plurality of heterogeneous monoclonal antibodies, i.e. individual monoclonal antibodies comprising the population may recognize antigenic determinants distinct from each other.

The claims are not drawn to extracting purified antigens for use as immunogens; the claims are simply drawn to introducing a "plurality of candidate antigens" into an animal for the production of a plurality of monoclonal antibodies.

> USPTO personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). Limitations appearing in the specification but not recited in the claim should not be read into the claim. E-Pass Techs., Inc. v. 3Com Corp., 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) (claims must be interpreted "in view of the specification" without importing limitations from the specification into the claims unnecessarily). In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-551 (CCPA 1969). See also In re Zletz, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) ("During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow.... The reason is simply that during patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed.... An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.").
> The Federal Circuit's en banc decision in Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005)expressly recognized that the USPTO employs the "broadest reasonable interpretation" standard: The Patent and Trademark Office ("PTO") determines the scope of

> claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "in light of the specification as it would be interpreted by one of ordinary skill in the art." In re Am. Acad. of Sci. Tech. Ctr., 367 F.3d 1359, 1364[, 70 USPQ2d 1827] (Fed. Cir. 2004). Indeed, the rules of the PTO require that application claims must "conform to the invention as set forth in the remainder of the specification and the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description." 37 CFR 1.75(d)(1).

Mather et al clearly read on such step of introducing or immunizing an animal with a "plurality of cells" (interpreted as candidate antigens) for the production of a plurality of monoclonal antibodies, in this case the antibodies bind to the cell surface antigens. Hence, the method taught by Mather et al is neither disadvantageous to a skilled artisan nor teach way from the invention as instantly claimed.

The references submitted by the applicant, De Masi et al and Chambers et al, are noted. The applicant states that these studies published well after the priority date for the present application attempts to solve the problem of developing a high-throughput method of producing polyclonal antibodies. Such arguments are not considered persuasive.

As stated earlier, the mere introduction of "high throughput method" for producing a plurality of monoclonal antibodies within the claims does not differentiate it from any other method of producing a plurality of monoclonal antibodies.

The applicant argues that the claimed methods enable the production and screening of monoclonal antibodies ... this advantage alone represents huge progress over methods of Kucherlapati" (page 17 of the response). This statement, however may be true, does not make the method of producing a plurality of monoclonal antibodies

novel because Mather et al clearly teach a method wherein a plurality of monoclonal antibodies can be produced and additionally screened for their specific antigens.

The applicant argues that there is no suggestion in any document that an improved method for producing and screening ... monoclonal antibodies against a plurality of candidate antigens ... obtained by immunizing an animals ... screening the monoclonal antibodies using protein chips (page 17 of the response). Again, the applicant is pointed to the studies of Rava et al which teaches methods for concurrently processing multiple assays by providing a biological chip plate comprising a plurality of test wells to detect reactions between target molecules and probes, wherein probe can be selected from proteins of interest and the targets can be selected from monoclonal antibodies. Thus, one of ordinary skill in the art would have been motivated to produce a plurality of monoclonal antibodies as taught by Mather et al and be able to screen the monoclonal antibodies using protein chips as taught by Rava et al.

The applicant states that Chambers et al, despite being published over a year after the priority date of the present application, this paper does not contemplate generating multiple monoclonal antibodies by immunizing with multiple antigens (page 18 of the response, in particular). It is brought to the applicants' attention that essence of Chambers et al's studies deal with the production of polyclonal antibodies by genetic immunization. Such method comprises delivering antigen-coding plasmid DNA into the animal, wherein the animal's cells produce the protein from the expression vectors, which stimulates the animal's immune system to produce antibodies against that

particular protein. Such is not at all the concern of the instantly claimed invention. The instant claims are drawn to the production of a plurality of monoclonal antibodies by introducing a plurality of candidate antigens into an animal, but not a gene or plasmid encoding an antigen. Hence, the arguments in regard to the success or motivation of Chambers et al is considered irrelevant.

> The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. In re Young, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991) (Prior art patent to Carlisle disclosed controlling and minimizing bubble oscillation for chemical explosives used in marine seismic exploration by spacing seismic sources close enough to allow the bubbles to intersect before reaching their maximum radius so the secondary pressure pulse was reduced. An article published several years later by Knudsen opined that the Carlisle technique does not yield appreciable improvement in bubble oscillation suppression. However, the article did not test the Carlisle technique under comparable conditions because Knudsen did not use Carlisle's spacing or seismic source. Furthermore, where the Knudsen model most closely approximated the patent technique there was a 30% reduction of the secondary pressure pulse. On these facts, the court found that the Knudsen article would not have deterred one of ordinary skill in the art from using the Carlisle patent teachings.).

It is further noted that the applicant admits that Kohler and Milstein's method of producing monoclonal antibodies disclosed in, for example Kucherlapati et al, had been known for over 25 years at the priority date. Protein chips had also been known before the priority date of the present application, as demonstrated by the disclosure of Rava et al. In view of the importance of monoclonal antibodies in molecular biology, the need to provide an improved, high-throughput method of producing monoclonal antibodies was apparent well before the priority date. However, despite the fact that methods of producing monoclonal antibodies here known and the existence of protein chips, no-one had considered combining these two techniques to produce a high throughput method of simultaneously producing monoclonal antibodies against a plurality of antigens, as

now claimed. This, in itself, suggests that the combination would not have been obvious to the skilled person at the priority date.

Such arguments are not considered persuasive. The applicants did not in any manner consider the studies published by Mather et al wherein the method of producing a plurality of monoclonal antibodies by immunizing an animal with a plurality of antigens, in addition to screening such monoclonal antibodies was clearly contemplated and successfully attempted. It is the examiners position that one of ordinary skill in the art would have been clearly motivated to combine the method of producing a plurality of monoclonal antibodies of Mather et al with that of Rava et al wherein protein chips were very well known to use for screening and identifying monoclonal antibodies to produce the claimed method.

Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
Parithosh K. Tungaturthi
Ph: (571) 272-8789

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER